DOI:10.1111/j.1365-2125.2005.02480.x

Suicide and self-harm following prescription of SSRIs and other antidepressants: confounding by indication

Rebecca C. Didham,[1] Doug W. McConnell,[1] Hayden J. Blair[1] & David M. Reith[2]

[1]*Research Unit, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand and* [2]*Dunedin School of Medicine, University of Otago, Dunedin, New Zealand*

Correspondence
David Reith, Department of Women's and Children's Health, Dunedin School of Medicine, University of Otago, PO Box 913, Dunedin, New Zealand.
Tel: +64 34740999 Ext 8226
Fax: +64 34747817
E-mail: david.reith@stonebow.otago.ac.nz

Received
9 January 2005
Accepted
11 May 2005

Aim
To identify the incidence and risk of suicide and self harm, among patients prescribed antidepressant drugs.

Methods
A retrospective cohort study, with nested case control, of patients identified from a nonrandom sample of general practices in New Zealand from 1996 to 2001. A total of 57 361 patients who received a prescription for a single antidepressant were identified from the RNZCGP Research Unit Database. Suicides within 120 days of a prescription were identified from the New Zealand National Mortality Database and self-harm events within 120 days of a prescription were identified from the New Zealand Hospital discharge database.

Results
26 suicides and 330 episodes of self-harm were identified within 120 days of an antidepressant prescription. On univariate analysis the association, expressed as OR (95% CI), between selective serotonin reuptake inhibitors (SSRIs) and self harm and suicide were 2.26 (1.27–4.76) and 1.92 (0.77–4.83), respectively. When corrected for the confounding effects of age, gender and depression/suicidal ideation there was an association between SSRIs and self harm, OR 1.66 (95% CI 1.23–2.23), but not for suicide, 1.28 (0.38–4.35). Paroxetine was a significant risk factor for suicide on univariate analysis, 4.23 (1.19–14.95), but not when corrected for age, gender and depression/suicidal ideation, 2.76 (0.30–24.87).

Conclusions
Age, gender and pre-existing depression/suicidal ideation are important confounders in observational studies of the association between antidepressants and suicide or self harm.

Introduction

Concerns have been raised about the potential for selective serotonin re-uptake inhibitors (SSRIs) to increase suicidal ideation [1]. In New Zealand the most widely prescribed antidepressant is paroxetine, with fluoxetine being the second most commonly prescribed antidepressant [2]. GlaxoSmithKline (GSK), the manufacturers of Aropax (paroxetine) conducted trials in paediatric and adolescent patients and found an increased risk of adverse effects, including treatment emergent suicidal ideation, but not completed suicide [3]. This has resulted in warnings against 'off-label' prescribing of paroxetine to patients under the age of 18 as well as a caution issued for close monitoring of both adults and paediatric

patients being treated with antidepressants [1, 3]. Associated changes have also been made to the labelling of paroxetine for dispensing.

However, evidence of an increased rate of completed suicides in association with the use of paroxetine, or other SSRIs is limited, and contradictory [4–6]. A recent study by Jick *et al.* found that the risk of suicidal behaviour among patients treated with amitriptyline, dothiepin, fluoxetine and paroxetine was similar [7]. A recent meta-analysis of randomized controlled trials indicated no increase in the risk of completed suicide for SSRIs compared with either TCAs or placebo [8]. However, the same study indicated an increased risk of suicide attempt with SSRIs compared with placebo but not compared with TCAs [8]. There is evidence that antidepressant drugs ameliorate suicidal tendencies, but also that treatment emergent suicidal ideation can occur [9]. It is thought that a therapeutic prescription of paroxetine in a depressed patient may actually initiate or increase suicidal ideation, as patients start to regain the 'initiative and energy that suicide requires' [10]. However, suicidal ideation is a surrogate measure for completed suicide, and there are limited data implicating SSRIs with increased rates of completed suicide [5].

SSRIs are commonly prescribed in New Zealand for the treatment of depression and other conditions, with paroxetine presently being the most frequently prescribed antidepressant [2]. An excess of poisoning deaths in association with paroxetine usage has not been demonstrated; in fact it appears that paroxetine has a similar rate of poisoning deaths as other SSRIs, and a lesser rate than tricyclic antidepressants [2]. Paroxetine has similar efficacy to other antidepressants commonly used in New Zealand, so any increased risk of suicide attributable to paroxetine use would indicate that other antidepressants should be used in preference. It is therefore important to determine whether there is an increased risk. The present study aimed to investigate this by analysing general practice patient and prescription data over a 5-year period, linking the data to mortality and hospital discharge records to identify suicide and self-harm events.

Methods

A cohort study was conducted using data-linkage between the Dunedin Royal New Zealand College of General Practitioners Research Unit (RNZCGPRU) database and both the New Zealand National Mortality Database and the New Zealand Hospital Separation Diagnosis Database (hospital discharges). A secondary case-control analysis was used to explore the contribution of potential confounders.

Computerized clinical records were accessed from the RNZCGPRU database. This database comprises a nonrandom sample of general practices, encompassing approximately 10% of the population of New Zealand each year, with a total of 1.4 million unique patient records between 1996 and 2003. Data include anonymized patient identifier codes, consultation dates and free text notes, prescribing dates and prescription details. All patients were selected for a 6-year period from 1 January 1996 to 31 December 2001, and then records were excluded where they did not contain a valid encrypted National Health Index number (eNHI) (a unique standardized patient identifier code), date of birth, or gender. Patients under the age of 10 years were also excluded. This resulted in a total population of 521 087. Patients who had been prescribed an antidepressant drug-SSRI, tricyclic antidepressant (TCA) or monoamine oxidase inhibitor (MAOI) at any time during the study period were selected from this population. Prescriptions were excluded where more than one antidepressant drug type was prescribed concurrently within the prescription period (90 days from prescription date). Some patients were included for more than one antidepressant type, if their prescription periods were not overlapping (>90 days between prescription dates).

The New Zealand National Mortality Database provided records of mortality for the years 1996–2001, including date of death and death type as recorded by International Classification of Disease (ICD) codes, ICD-9 (1996–99) and ICD-10 (2000–2001). The classification of death is based on final coroner reports and follows WHO Rules and Guidelines for Mortality Coding. The study cohort were linked to this database by their eNHI number. Those patients with a recorded death by suicide were identified using the corresponding ICD-9 codes. Mortality data listed using ICD-10 codes were mapped back to ICD-9 codes for consistency, according to documentation provided by the New Zealand Health Information Service. The resulting group of patients were linked back to their prescription information to identify the suicide deaths that occurred within 60, 90 and 120 days of a single antidepressant prescription.

Hospital discharge information from 1996 to 2001 was obtained from the New Zealand Hospital Separation Diagnosis Database. This database includes date of admission, date of event and event type/treatment details as categorized by ICD codes. The study group patients were linked to this database by eNHI number to identify any who had been admitted for a self-harm event as identified by ICD-9 code. These patients were linked back to their prescription information to identify any

self-harm events that occurred within 60, 90 and 120 days of prescription.

Nested case control studies were performed separately for suicide and for self harm. For the suicide outcome measure, the cases (patients who committed suicide or self harm within 60, 90 and 120 days post prescription) were matched 1 : 3 by month and year of their last prescription, to a random sample of all patients prescribed antidepressants. Clinical notes on the date of prescription, plus 90 days prior were studied for a diagnosis of depression (as recorded by the GP) and mentions of suicidal ideation. Hospital discharge information was also studied for any events of depression (as classified by ICD code) in the 90 days prior to prescription. This method was then repeated for the group of patients with a self-harm event, who were also matched 1 : 3, by prescription date, to a random sample of all patients prescribed antidepressants. The same variables were collected – GP diagnosis of depression and note of suicidal ideation, and hospitalized depressive events.

For the cohort study, incidence rates for suicide and self-harm were calculated and their 95% CI determined using the Poisson distribution. For the nested case-control studies, OR (95% CI) for univariate analysis were determined using conditional logistic regression. Corrected OR (95% CI) were determined using multivariate conditional logistic regression with the variables gender, age >50 years and GP notation of depression or suicidal ideation included in each model. The cases and their matched triplicates were used as the grouping variable. All statistical analyses were performed using Stata® version 8 [11].

Results

A total of 57 361 unique patients (a total of 65 293 when patients are counted for more than one drug type) were identified as having 138 241 prescription periods for a single antidepressant drug between 1996 and 2001. Of these, 39 012 (68.01%) were female and the median (range) age was 46 (10–102) years. The most frequently prescribed antidepressants to the patient group were fluoxetine, amitriptyline and paroxetine (Table 1). A total of 65 patients from the cohort committed suicide and of these, 26 committed suicide within 120 days of a single antidepressant prescription. Eighteen (69.2%) of these patients were male. The median age (range) for the patients who committed suicide was 40 (22–81) years. The methods of suicide were: carbon monoxide gas (8), hanging/strangling/suffocation (7), drug overdose (6), drowning (2), jumping/lying before moving object (1), firearm (1) and conflagration (1). The incidence rates for suicide indicated no significant differences between SSRIs and TCAs at 60, 90 and 120 days (Table 1).

Of the 26 suicides, only one patient had a prior history of self harm within the study period. Five of these patients had a hospital admission for depression prior to committing suicide and general practitioners recorded the presence of suicidal ideation in six of these patients

Table 1
Rates of suicide following last recorded antidepressant prescription

Antidepressant	Prescription periods	60 days *n*	60 days Incidence rate per 10 000 prescription periods (95% CI)	90 days *n*	90 days Incidence rate per 10 000 prescription periods (95% CI)	120 days *n*	120 days Incidence rate per 10 000 prescription periods (95% CI)
Citalopram	3808	0	0.00 (0.00–9.68)	0	0.00 (0.00–9.68)	0	0.00 (0.00–9.68)
Fluoxetine	32 591	3	0.92 (0.19–2.69)	6	1.84 (0.68–4.01)	6	1.84 (0.68–4.01)
Paroxetine	21 895	4	1.83 (0.50–4.68)	7	3.20 (1.29–6.59)	7	3.20 (1.29–6.59)
SSRI	58 688	7	1.19 (0.48–2.46)	13	2.22 (1.18–3.79)	13	2.22 (1.18–3.79)
Amitriptyline	29 814	1	0.34 (0.01–1.87)	1	0.34 (0.01–1.87)	2	0.67 (0.08–2.42)
Clomipramine	2444	3	12.28 (2.53–35.86)	3	12.28 (2.53–35.86)	3	12.28 (2.53–35.86)
Dothiepin	13 032	2	1.54 (0.19–5.54)	2	1.54 (0.19–5.54)	2	1.54 (0.19–5.54)
Doxepin	15 219	3	1.97 (0.41–5.76)	3	1.97 (0.41–5.76)	4	2.63 (0.72–6.73)
Imipramine	3761	0	0.00 (0.00–9.81)	0	0.00 (0.00–9.81)	0	0.00 (0.00–9.81)
Nortriptyline	6514	1	1.54 (0.04–8.55)	1	1.54 (0.04–8.55)	1	1.54 (0.04–8.55)
Trimipramine	3760	1	2.66 (0.07–14.82)	1	2.66 (0.07–14.82)	1	2.66 (0.07–14.82)
TCA	75 811	11	1.45 (0.72–2.60)	11	1.45 (0.72–2.60)	13	1.71 (0.91–2.93)
Moclobemide	3360	0	0.00 (0.00–10.98)	0	0.00 (0.00–10.98)	0	0.00 (0.00–10.98)
MAOI	3742	0	0.00 (0.00–9.86)	0	0.00 (0.00–9.86)	0	0.00 (0.00–9.86)
Total	13 8241	18	1.30 (0.77–2.06)	24	1.74 (1.11–2.58)	26	1.88 (1.23–2.76)

in the 90 days prior to their last prescription. Univariate analysis indicated a significantly increased risk for suicide if patients were male, had a general practice notation of depression or suicidal ideation or were prescribed paroxetine (Table 3). However, on multivariate analysis the corrected OR (95% CI) for paroxetine at 120 days was 2.76 (0.47–10.72), with similar findings at 60 and 90 days (Table 4).

Of the 138 241 prescription periods (120 days) for a single antidepressant, 330 resulted in a self-harm event. Of the 330 incidences of self harm, 229 (69.4%) occurred in females, with a mean age (range) of 35 (13–92) years, and 101 (30.6%) occurred in males, with a mean age of 35 (15–83) years. The methods of self harm included: drug overdose (275), self-inflicted cutting injury (27), ingestion of a toxic substance (11), carbon monoxide gas (11), jumping/lying before moving object (1), hanging/strangling/suffocation (1), burns (1), and motor vehicle (1). There were significantly increased incidence rates for self harm with SSRIs as a group compared with TCAs, incidence rate ratio (95% CI) 2.57 (2.03–3.28). There were similar rates of self harm for the three SSRIs examined in the study (Table 2).

The case-control data indicated an increased risk of self harm for SSRIs as a group, and fluoxetine, paroxetine and citalopram individually, on univariate analysis (Table 3). Age <50 years and a general practice notation of depression or suicidal ideation were also risk factors. Multivariate analysis indicated a decreased strength of association, although still statistically significant, for SSRIs with self harm of 1.66 (1.23–2.23) at 120 days, with similar findings at 60 and 90 days (Table 4).

Discussion

The present study demonstrates the limitations of observational studies in determining an association between a treatment and an outcome when the outcome itself is strongly associated with the condition being treated. Confounding by indication, whereby patients are selected for a particular treatment depending upon their diagnosis, or the severity of their medical condition, may lead to erroneous conclusions of a treatment resulting in an adverse outcome [12]. Although the present study apparently demonstrated an association between SSRIs and self-harm, when corrected for diagnosis and severity there was no association between SSRIs as a group or individually with suicide and a decreased strength of association with self harm. Instead factors such as age, gender, suicidal ideation and depression itself appeared to be the primary risk factors for these outcomes. This suggests prescribers are preferentially prescribing SSRIs, and in particular the newer SSRIs, to patients with a greater risk of suicide or self harm, while

Table 2
Rates of self harm leading to hospital admission following last recorded antidepressant prescription

Drug name	Prescription periods	60 days *n*	60 days Incidence rate per 10 000 prescription periods (95% CI)	90 days *n*	90 days Incidence rate per 10 000 prescription periods (95% CI)	120 days *n*	120 days Incidence rate per 10 000 prescription periods (95% CI)
Citalopram	3 808	13	34.18 (18.20–58.45)	15	39.39 (22.05–64.67)	17	44.70 (26.04–71.57)
Fluoxetine	32 591	78	23.93 (18.92–29.87)	100	30.68 (24.96–37.32)	116	35.59 (29.41–42.69)
Paroxetine	21 895	57	26.03 (19.72–33.73)	68	31.06 (24.12–39.37)	75	34.25 (26.94–42.94)
All SSRIs	58 688	150	25.56 (21.63–29.99)	186	31.69 (27.30–36.59)	211	35.95 (31.26–41.14)
Amitriptyline	29 814	23	7.71 (4.89–11.57)	28	9.39 (6.24–13.57)	34	11.40 (7.90–15.94)
Amoxapine	818	1	12.22 (0.31–68.11)	1	12.22 (0.31–68.11)	1	12.22 (0.31–68.11)
Clomipramine	2 438	5	20.51 (6.66–47.85)	6	24.61 (9.03–53.56)	7	28.71 (11.54–59.15)
Dothiepin	13 032	12	9.21 (4.76–16.08)	12	9.21 (4.76–16.08)	14	10.74 (5.87–18.02)
Doxepin	15 219	15	9.86 (5.52–16.26)	22	14.46 (9.06–21.89)	25	16.42 (10.63–24.25)
Imipramine	3 761	4	10.63 (2.90–27.23)	6	15.95 (5.85–34.72)	7	18.61 (7.48–38.34)
Nortriptyline	6 514	4	6.14 (1.67–15.72)	8	12.28 (5.30–24.20)	8	12.28 (5.30–24.20)
Trimipramine	3 760	7	18.62 (7.48–38.35)	8	21.28 (9.19–41.92)	8	21.28 (9.19–41.92)
All TCAs	75 811	72	9.50 (7.43–11.96)	93	12.27 (9.90–15.03)	106	13.98 (11.45–16.91)
Moclobemide	3 360	8	23.81 (10.28–46.91)	12	35.71 (18.46–62.38)	13	38.69 (20.60–66.16)
All MAOIs	3 742	8	21.38 (9.23–42.12)	12	32.07 (16.57–56.01)	13	34.74 (18.50–59.41)
Total	138 241	230	16.64 (14.56–18.93)	291	21.05 (18.70–23.61)	330	23.87 (21.36–26.59)

Table 3
Case control results: suicide and self-harm at 120 days, unadjusted OR (95% CI)

Exposure	Case, *n* (%)	Control, *n* (%)	Odds ratio (95% CI)	Case, *n* (%)	Control, *n* (%)	Odds ratio (95% CI)
Male gender	18 (69.2)	20 (25.6)	5.49 (2.10–14.32)	101 (30.6)	309 (31.2)	0.97 (0.74–1.27)
Age >50 years	7 (26.9)	37 (47.4)	0.43 (0.17–1.10)	48 (14.5)	451 (45.6)	0.20 (0.14–0.29)
Amitriptyline	2 (7.69)	22 (28.2)	0.22 (0.05–1.0)	34 (10.3)	192 (19.4)	0.47 (0.31–0.69)
Clomipramine	3 (11.5)	1 (1.3)	9.0 (0.94–86.52)	8 (2.4)	19 (1.9)	1.26 (0.55–2.88)
Dothiepin	2 (7.7)	8 (10.3)	0.70 (0.13–3.82)	14 (4.2)	97 (9.8)	0.41 (0.23–0.73)
Doxepin	4 (15.4)	13 (16.7)	0.91 (0.27–3.07)	25 (7.6)	95 (9.6)	0.76 (0.48–1.22)
Fluoxetine	6 (23.1)	18 (23.1)	1.0 (0.35–2.85)	115 (34.8)	261 (26.4)	1.53 (1.16–2.02)
Nortriptyline	1 (3.8)	3 (3.8)	1.0 (0.10–9.61)	8 (2.4)	57 (5.8)	0.38 (0.17–0.82)
Paroxetine	7 (26.9)	7 (9.0)	4.23 (1.19–14.95)	75 (22.7)	156 (15.8)	1.62 (1.18–2.23)
Trimipramine	1 (3.8)	2 (2.6)	1.5 (0.14–16.54)	8 (2.4)	17 (1.7)	1.41 (0.61–3.27)
Citalopram	0 (0)	2 (2.6)	NA	17 (5.1)	22 (2.2)	2.46 (1.27–4.76)
Moclobemide	0 (0)	1 (1.3)	NA	13 (3.9)	39 (3.9)	1.0 (0.51–1.96)
Imipramine	0 (0)	1 (1.3)	NA	7 (2.1)	26 (2.6)	0.80 (0.35–1.87)
SSRI	13 (50.0)	27 (34.6)	1.92 (0.77–4.83)	207 (62.7)	439 (44.3)	2.26 (1.72–2.96)
TCA	13 (50.0)	50 (64.1)	0.55 (0.22–1.38)	106 (32.1)	506 (51.1)	0.42 (0.31–0.55)
MAOI	0 (0)	1 (1.3)	NA	13 (3.9)	41 (4.1)	0.94 (0.48–1.84)
Note of depression/ideation	13 (50.0)	10 (12.8)	7.12 (2.27–22.32)	89 (27.0)	75 (7.58)	4.38 (3.10–6.18)

Table 4
Case-control results: risk for suicide, OR (95% CI), by prescribed antidepressant, corrected for gender, age and GP notation

Variable	60 days	90 days	120 days
Suicide			
SSRI	0.63 (0.14–2.86)	1.43 (0.41–4.99)	1.28 (0.38–4.35)
Fluoxetine	0.35 (0.06–2.09)	0.89 (0.24–3.31)	0.80 (0.22–2.89)
Paroxetine	2.76 (0.30–24.87)	2.20 (0.47–10.32)	2.25 (0.47–10.72)
TCA	1.58 (0.35–7.16)	0.90 (0.25–3.24)	1.0 (0.28–3.53)
Amitriptyline	0.12 (0.01–1.52)	0.12 (0.01–1.36)	0.21 (0.03–1.52)
Self harm			
SSRI	1.83 (1.28–2.61)	1.74 (1.26–2.38)	1.66 (1.23–2.23)
Fluoxetine	1.47 (1.03–2.11)	1.39 (1.01–1.91)	1.30 (0.96–1.75)
Paroxetine	1.08 (0.72–1.61)	1.06 (0.73–1.54)	1.21 (0.84–1.72)
TCA	0.53 (0.37–0.75)	0.54 (0.39–0.74)	0.54 (0.40–0.74)
Amitriptyline	0.54 (0.32–0.89)	0.55 (0.34–0.86)	0.59 (0.38–0.90)

TCAs are being prescribed to patients without depression necessarily being the indication.

In order to determine if paroxetine, or other newer SSRIs, are associated with an increased risk of suicide or self harm would require a large randomized controlled trial. Using the incidence rates from the present study, to determine if there is a doubling of risk of self harm would require a sample size of 1675 (alpha = 0.05, power = 0.9) in each treatment group. To determine if there is a doubling of the risk of suicide would require a sample size of 192 436 in each treatment group. These sample sizes are conservative estimates because RCTs of antidepressants often exclude those patients at greatest risk of suicide or self harm [13] and the New Zealand population (used to determine the sample size) has a relatively high rate of suicide [14]. Hence, although it may be possible to conduct RCTs using surrogate end points of suicide, such as self harm or suicidal ideation, it is unlikely that an RCT using suicide as an endpoint will ever be conducted.

Jick *et al.* (2004) attempted to correct for confounding by indication by only including patients having their

first course of antidepressant treatment [7]. However this approach may not be successful because it is not always possible to confirm that a patient has not previously been treated with antidepressants. Antidepressant medication may have previously been commenced by a healthcare provider who did not contribute data to the study, such as an inpatient or outpatient psychiatric unit or a primary care provider in a different region. In addition, suicide may be the endpoint of a chronic illness rather than an acute illness and excluding patients with prior history of antidepressant prescription, depression or self harm ignores the very population that most requires investigation [15]. In contrast, the approach used in the present study was to correct for confounding by indication by using multivariate analysis [12].

New Zealand has rates of suicide in the general population which are higher compared with those of the USA, UK and Australia [14]. Latest figures show that the rate of suicide among the general population of New Zealand in 2001, was 11.7 deaths per 100 000 population [16]. The proportion of suicide deaths that were males in New Zealand in 2001 was 76.6% [16] which is greater than the proportion of 69.2% male gender for suicide concurrent to an antidepressant drug in this study, however, a lesser proportion of males were prescribed antidepressants. The risk factors for suicide suggested by the present study were male gender and depression and/or self harm and/or suicidal ideation.

Previous observational studies in a UK population have examined the relationship between SSRIs and self harm [7, 17, 18]. A retrospective cohort study relating hospital attendances with self harm to prescription rates in the general population found that the relative incidence of self harm was higher for patients prescribed SSRIs than for those prescribed TCAs [17]. A matched case control study using a general practice database examined first prescription of antidepressant and first presentation with self harm and found that there was no significant association between the use of a particular antidepressant and the risk of self harm [7]. Neither study examined known risk factors for self harm, although Jick *et al.* (2004) controlled, to some extent, for the effects of disease severity by only examining first prescription with antidepressant. Martinez *et al.* 2005 did correct for the confounding effect of a diagnosis of depression and found an overall adjusted odds ratio of nonfatal self-harm (for patients prescribed SSRIs compared with those prescribed TCAs) of 0.99 (0.86–1.14) and for suicide of 0.57 (0.26–1.25) [18]. Similarly, in the present study, using multivariate analysis, the risk factor for suicide were gender and depression and/or suicidal ideation rather than choice of antidepressant.

Studies in children and adolescents which indicated increased treatment emergent suicidal ideation in association with SSRIs had rigorous exclusion criteria, including prior suicidal ideation or behaviour [19, 20]. A previous meta-analysis of suicidality with fluoxetine treatment indicted no increase in self harm in patients treated with fluoxetine, compared with placebo or TCA, and a decrease in suicidal ideation [4]. However, prescribers may be preferentially prescribing SSRIs for patients with risk factors for self harm, either clearly identifiable or subtle, because of a better safety profile in overdose [2]. Given their toxicity in overdose a prescriber would be unlikely to prescribe a TCA in preference to a SSRI to a patient who was considered to be at risk of self harm. Thus, confounding by indication gives the appearance of SSRIs increasing self harm, which in an observational study can only be corrected by including diagnosis and/or disease severity in a multivariate analysis.

A limitation of studies that use sampling strategies such as the RNZCGPRU database, is that there are issues of validity and bias associated with the data from contributors to such groups. The morbidity in patients in the practices included in the RNZCGPRU database is not different from that in other patients from the general population [21]. In addition data recorded by contributing practices is relatively complete [22]. It can therefore be reasonably assumed that the dataset used in the present study is representative of patients prescribed antidepressant drugs in the general New Zealand population. An additional limitation of the present study was the inclusion of only those self-harm events that required hospitalization. It is recognized that a large proportion of intentional self-harm episodes may be treated in emergency departments without admission; at general practice surgeries; or may not receive treatment at all. A further limitation was the assumption made that patients complied with their prescribing advice, even though this may not be true for patients taking antidepressant drugs. However, for the suicide patients in this study, most events occurred after a history of more than one prescription, implying a likelihood of compliance. Any prescriptions for drug types other than antidepressants were disregarded, as was the history of self harm, depression and suicidal ideation prior to the period of this study. One of the most obvious limitations of this study is the small numbers involved in the analysis of suicide. Suicide is a rare event and even using a very large cohort, such as in this study, the number of completed suicides is always going to be very small, limiting the strength of statistical results. An important consideration is that the

present study did not compare either SSRIs or TCAs with placebo or no treatment.

Overall the results of this study suggest that the more depressed patients are prescribed SSRIs, therefore these drugs appear to show a greater risk of self-harm and suicide. However the real risk factors are more likely to be depression and suicidal ideation. The effects of antidepressant medication upon completed suicide should be further explored using RCTs, and using self harm as a surrogate outcome measure.

We wish to thank the participating general practices from the RNZCGPRU database for contributing their records and allowing them to be used for research purposes. We also thank Brendan Ward for designing the computer programming for the case control analysis and Ken Harrison for his work on previous analyses.

Funding: The Royal New Zealand College of General Practitioners Research Unit receives financial support from the New Zealand Government.

References

1 Waechter F. Paroxetine must not be given to patients under 18. BMJ 2003; 326 (7402): 1282.

2 Reith D, Fountain J, Tilyard M, McDowell R. Antidepressant poisoning deaths in New Zealand for 2001. NZ Med J 2003; 116 (1184) (U646): 1–7.

3 GlaxoSmithKline Inc. Paroxetine and pediatric and adolescent clinical trial data. http://www.gsk.com/media/paroxetine.htm. 24th November 2004.

4 Beasley CM, Dornseif BE, Bosomworth JC, Sayler ME, Rampey AH, Heiligenstein JH, Thompson VL, Murphy DJ, Masica DN. Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. BMJ 1991; 303 (6804): 1058–9.

5 Jick SS, Dean AD, Jick H. Antidepressants and suicide. BMJ 1995; 310 (6974): 215–8.

6 Khan A, Khan S, Kolts R, Brown WA. Suicide rates in clinical trials of SSRIs, other antidepressants, and placebo: analysis of FDA reports. Am J Psychiatry 2003; 160 (4): 790–2.

7 Jick H, Kaye J, Jick S. Antidepressants and the risk of suicidal behaviours. JAMA 2004; 292 (3): 338–42.

8 Fergusson D, Doucette S, Glass KC, Shapiro S, Healy D, Hebert P, Hutton B. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. BMJ 2005; 330 (7488): 396.

9 Teicher MH, Glod CA, Cole JO. Antidepressant drugs and the emergence of suicidal tendencies. Drug Saf 1993; 8 (3): 186–212.

10 Szanto K, Mulsant B, Houck P, Dew M, Reynolds C. Occurrence and course of suicidality during short-term treatment of late-life depression. Arch Gen Psychiatry 2003; 60 (6): 610–7.

11 Stata Corporation. Intercooled STATA 8.0 for Windows 8.0. College Station: Stata Corporation, 2003.

12 Grimes D, Schulz K. Bias and causal associations in observational research. Lancet 2002; 359: 248–52.

13 Keitner G, Posternak M, Ryan C. How many subjects with major depressive disorder meet eligibility requirements of an antidepressant efficacy trial? J Clin Psychiatry 2003; 64 (9): 1091–3.

14 Levi F, La Vecchia C, Lucchini F, Negri E, Saxena S, Maulik P, Saraceno B. Trends in mortality from suicide, 1965–99. Acta Psychiatr Scand 2003; 108 (5): 341–9.

15 Carter G, Reith DM, Whyte IM, McPherson M. Repeat self-poisoning patients: increasing severity of self-harm is predictive of subsequent suicide. Br J Psychiatry 2005; 186: 253–7.

16 Ministry of Health. Suicide Facts: Provisional 2000 Statistics (all ages). Wellington: Ministry of Health, 2003.

17 Donovan S, Clayton A, Beeharry M, Jones S, Kirk C, Waters K, Gardner D, Faulding J, Madeley R. Deliberate self-harm and antidepressant drugs – Investigation of a possible link. Br J Psychiatry 2000; 177: 551–6.

18 Martinez C, Rietbrock S, Wise L, Ashby D, Chick J, Moseley J, Evans S, Gunnell D. Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study. BMJ 2005; 330 (7488): 389.

19 SmithKline Beecham. A double-blind, multicentre placebo controlled study of paroxetine in adolescents with unipolar major depression. SB Document number BRL-029060/RSD-100TNP/2; 1998.

20 SmithKline Beecham. A randomised, multicenter, 8-week, double-blind, placebo-controlled flexible dose study to evaluate the efficacy and safety of paroxetine in children and adolescents with major depressive disorder. SB Document number: BRL-029060/RSD-101C0C/1; 2001.

21 Tilyard M, Dovey S, Spears G. Biases in estimates from the RNZCGP computer research group. NZ Med J 1995; 108: 118–21.

22 Hall J, Tomlin A, Martin I, Tilyard M. A general practice minimum data set for New Zealand. NZ Med J 2002; 115 (1163): 1–7.